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Orphan Drugs

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Abstract: ***An orphan drug is a pharmaceutical agent that is used to treat a rare medical condition (viz., Huntington's disease, myoclonus disease, Tourette syndrome etc.). They receive little attention from pharmaceutical companies as the small patient population could not justify the huge investment required for drug development. In the last 20 years, orphan drug act has been adopted in several countries around the world (USA, Japan, Australia, and the EU) and has successfully promoted R&D investments to develop new pharmaceutical products for the treatment of rare diseases, but it faces future challenges like returns on the huge R & D costs, funding sources and initiatives for development of orphan drugs.***

Keywords: Rare disease, Orphan drugs, ODA

1. Introduction

Estimates vary but it is thought that between 5000-8000 rare diseases have been identified worldwide. There are different estimates as to how many patients are there who suffer from rare diseases but it is thought that there are at least 55 million patients with a rare disease in the EU and USAalthough some of the diseases are extremely rarewith only a few hundred patients affected. Examples of these are Hutchinson-Gilford Progeria Syndrome often referred to as progeria which causes a person to age prematurely. Creutzfeldt–Jakob disease which is a fatal brain disease and lymphangioleiomyomatosis which is a rare but fatal lung disease.

Clearly all patients should have the right to treatment irrespective of frequency of disease and indeed in the universal declaration of human rights adopted in 1948, it states in article 25 (1) - Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control

Following the increase in public awareness by rare disease patient organizations, the US Congress and senate realized the huge unmet medical demand for patients with rare diseases and the orphan drug legislation was born.

The term 'orphan drugs' and 'orphan diseases' come from the Greek word 'orphanos' which means a child who has lost one or both parents or an adult who has lost a child. So the reason for naming drugs for rare diseases as orphan drugs is that they are 'very much like children who has no parents and they require special effort and becausein the past no drug company wanted to 'adopt' it.[1]

Definition of rare disease:
WHO defines rare disease as a disease or condition with a prevalence of ≤1/1000 population.[1] Other definitions are diseases affecting <1/2000 population in European union, whereas USFDA defines it as any disorder affecting <200,000 population at a single time point.[2] Ultra rare disease is a disease affecting <2 patients/100,000population. However, rare diseases are indeed not so rare. As most of definitions are based on the prevalence of disease, the orphan disease burden is high in countries with high population. A disease can be rare in a region but may be very common in another region, for example, IgA nephropathy is common in Asia and Africa, but rare in European Union. Lots of issues complicate the drug development process of rare diseases, for example, less understood pathophysiology, lack of validated preclinical models, less research, and lack of standard comparator drug. Clinical issues such as lack of information about natural history of the disease, poorly defined endpoints, poor trial design and inadequate sample size, recruitment problems, lack of well-defined diagnostic criteria, and other issues such as nonexistent comparator drug and funding problems.[2]

Evolution of Orphan Drug Act (ODA): Because orphan drugs target small populations and yield lower returns, Asbury (1992) finds only four drugs that were on the market to treat rare diseases by 1965. Legislation significantly increased the costs associated with drug development and caused pharmaceutical companies to focus their attention on drugs that would maximize profits and the possibility of recouping their R and D costs.

Many people considered rare diseases to be "orphaned" or essentially ignored by drug manufacturers, due to the focus on profitable "blockbuster" treatments, defined as drugs that are expected to generate over $1 billion in sales annually. Because of their neglect, these treatments earned the label "orphan drug." Eventually, the influence of non-governmental organizations, like the National Organization for Rare Disorders (NORD) and patient advocacy groups made orphan drug development a focus of public policy in the late 1970s and early 1980s. In 1980 Congress implemented the Bayh-Dole Act (PL No. 96-517, 1984), allowing the recipients of government-sponsored R and D to patent and licensed their research followed by the Orphan Drug Act in 1983.

The Orphan Drug Act (ODA) of 1983: Before the Orphan Drug Act (ODA) of 1983, the FDA had approved only 58 orphan designations, with fewer than 10 approved in the decade before the ODA was passed (Pharma, 2013). After the ODA, existing drugs that qualified had to be reapproved to gain market exclusivity and the benefits of the Act. The

ODA has several parts, but its main purpose is to reduce costs and increase the returns to orphan drug production. Additionally, the ODA allows the FDA to expedite orphan drug designation approvals over other drugs, reducing the development time. In 1997 Congress made a 50% tax credit on R and D expenditures a permanent feature of the Act. This credit goes towards clinical trial expenses of drugs that have received official orphan drug status by the FDA. The most contested provision of the ODA is the seven years of market exclusivity rights that pharmaceutical companies can obtain for orphan products, which grants them a monopoly over the marketing of the drug for a particular indication.

Since the act has been enacted, it has been amended for numerous times by Congress. Initially, orphan status was only granted to drug manufacturers that demonstrated that the development of an orphan drug would be unprofitable and the costs would not be recouped through US sales. Orphan drugs could be profitable through worldwide sales as long as there were no "reasonable expectation" that US sales would exceed the development costs. Orphan drug exclusivity status was restricted to drugs that could not be patented, as some biotech drugs had difficulty in obtaining patents.

However, in 1985 another amendment to the ODA dropped that restriction. In reality, most orphan products could obtain patents, but it was because of the lengthy approval process that many of the patents expired before the product was able to reach the market, making them redundant. In 1990 Congress passed a proposal to limit market exclusivity, but President George H. W. Bush vetoed the amendment. Most recently, the FDA amended the ODA on June 12, 2013, to "clarify, streamline, and improve the orphan drug designation process" [3].

Definition of orphan disease in different countries:
There is currently no global international harmonization between countries or regions regarding the cut-off level for a disease to be considered orphan.
Some examples of the cut-off level for prevalence figures for a rare disease to be considered orphan disease are as follows:

- In the USA, the disease has to affect fewer than 200,000 patients or less than 7.5 in 10000.
- Japan has a cut-off level of fewer than 50,000 or fewer than 4 patients in 10,000.
- Australia fewer than 200 patients or fewer than 1.1 in 10,000.
- EU fewer than 5 in 10,000.

Canada not more than 5 per 10,000 inhabitants.[4]

Definition of orphan drug:
An orphan drug is defined in the 1984 amendments of the U.S. Orphan Drug Act (ODA) as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA.[5]

The spiraling cost of drug development in tune with stringent regulations, coupled with the low return on investment, often tends to discourage pharmaceutical innovators from developing products for extremely small patient populations. 80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies or are due to degenerative and proliferative causes.

Orphan drugs are an important public health issue and a challenge for the medical community. Modern society still has a lack of options for the effective treatment of patients with rare diseases. As one of the consequences of this, the demand for public health protection has increased the economic burden of a patient suffering from such diseases. Scientific advances have given researchers a new tool to explore these orphan diseases, which are often more complex than common diseases. On the brighter side, these rare diseases when taken together cannot be called rare at all. There are approximately 7000 different types of rare diseases and disorders with more being discovered today. It has been reported that there are about 250 new rare cases reported every year, however, the acceptable treatment is available only for 200-300 orphan diseases. It is known that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unknown origin. Overall orphan diseases are often chronic, progressive, disabling; even life-threatening and most of these have effective or curative treatment, having low prevalence and high complexity
.

Marketing Exclusivity: Orphan drug exclusivity applies to those vaccines and diagnostic or preventive drugs either designed to affect conditions that afflict a relatively small number of people or for which there is no reasonable expectation of the recovery of research and development costs. The approval of an application for orphan designation is based upon the information submitted by the sponsor. A drug that has obtained orphan designation is said to have "orphan status". Sponsors need to follow the "standard regulatory requirements and process for obtaining market approval" [13]. A sponsor may request orphan drug designation for a previously unapproved drug or an already marketed drug. More than one sponsor may receive orphan drug designation for the same drug for the same rare disease or condition. A drug with orphan status enjoys exclusive approval and market exclusivity.

Worldwide Sales: Over the five years to 2017, industry revenue is anticipated to grow at an annualized rate of 2.1% to $1.2 trillion, including 2.7% revenue growth in 2017 that was realized.

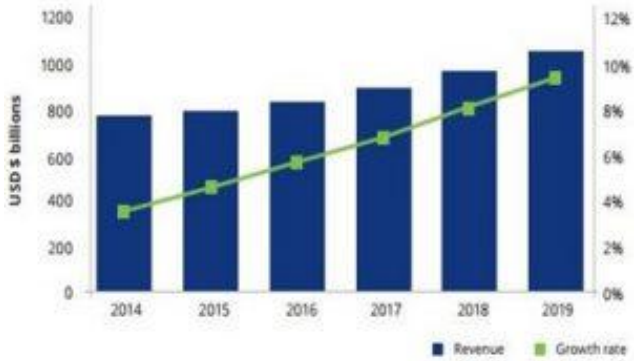

Figure 4: Worldwide Pharmaceuticals Sales, 2011- 2020

As more pharmaceutical manufacturers expand to serve emerging markets, industry revenue is expected to grow, especially as manufacturers target prevalent region-specific diseases. Profit is increased from 22.9% of industry revenue in 2012 to 24.1% in 2017, driven by rising global consumer demand for high-margin biologic drugs.

Global Trade and Regulations: The industry contended with global governments seeking to reduce drug costs. This trend has been particularly popular in Europe, with austerity measures resulting in many countries announcing reimbursement reductions. In response, many pharmaceutical companies have altered their drug portfolios from primary-care blockbusters to specialties such as oncology, immunology, and inflammation, where the medical need is so high that regulators more-readily accept prices.

Table 1: Revenue Growth

Year	Revenue (in mm)	Growth (%)
2007	8,67,156	
2008	9,05,801	4.46
2009	9,56,928	5.64
2010	10,07,008	5.23
2011	10,50,625	4.33
2012	10,42,338	-0.79
2013	10,51,157	0.85
2014	10,47,579	-0.34%
2015	11,03,644	5.35%
2016	11,26,549	2.08%
2017	11,56,516	2.66%

While this trend provided the industry with stable need-based demand, counterfeit drugs have hampered industry revenue growth. According to the World Health Organization, counterfeit drugs currently account for 10.0% of the global market, but in some emerging countries, this proportion is as high as 30.0% to 40.0%. Recent data from the World Customs Organization puts the drug counterfeiting business at $250.0 billion a year. Protection and enforcement of intellectual property rights remain a difficult issue in many emerging markets, with forgery and first-copy products widespread.

Table 2: List of Approved Orphan Drugs, 2018

Trade Name	Generic Name	Company	Designation	Indication	Marketing Approval Date
Azedra Ultratrace	Iobenguane I 131	Progenics Pharmaceutical, Inc.	Treatment of neuroendocrine tumors	AZEDRA is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy	07/30/2018
Omegaven	Omegaven emulsion	Fresenius Kabi USA, LLC	Treatment of parenteral nutrition-associated liver disease	Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)	7/27/2018
n/a	Tafenoquine	Glaxo Group Limited, England	Treatment of malaria	KRINTAFEL is indicated for the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection	7/20/2018
n/a	Ivosidenib	Agios Pharmaceutical, Inc.	Treatment of acute myeloid leukemia (AML)	TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test	7/20/2018
n/a	Gemcitabine ready-to-use	Sun Pharmaceutical Industries Ltd.	Treatment of ovarian cancer	INFUGEM in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy	7/16/2018
Tpoxx	Tecovirimat	SIGA Technologies, Inc.	Treatment of smallpox	TPOXX® is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 13 kg	7/13/2018
Signifor	Pasireotide	Novartis Pharmaceuticals Corporation	Treatment of Cushing's disease	SIGNIFOR® LAR is indicated for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative	6/29/2018
n/a	Encorafenib + binimetinib	Array BioPharma, Inc.	Treatment of Stage IIB-IV melanoma positive for the BRAF mutation.	BRAFTOVI™ is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as	6/27/2018

				detected by an FDA-approved test	
n/a	Encorafenib + binimetinib	Array BioPharma, Inc.	IIB-IV melanoma is positive for the BRAF mutation.	MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test	6/27/2018
Epidiolex	cannabidiol	GW Research Ltd.	Treatment of Lennox-Gastaut syndrome	EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older	6/25/2018
Epidiolex	Cannabidiol	GW Research Ltd.	Treatment of Dravet syndrome	EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older	6/25/2018
Ablysinol	Dehydrated alcohol	Belcher Pharmaceutical, LLC	Treatment of hypertrophic obstructive cardiomyopathy	ABLYSINOL® is indicated to induce controlled cardiac septal infarction to improve exercise capacity in adults with symptomatic hypertrophic obstructive cardiomyopathy who are not candidates for surgical myectomy	6/21/2018
Cinryze (R)	C1 esterase inhibitor (human)	ViroPharma Biologics, Inc.	Treatment of angioedema	CINRYZE is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years old and above) with Hereditary Angioedema (HAE)	6/20/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of fallopian tube carcinoma	the combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of patients with ovarian cancer	In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Keytruda	Pembrolizumab	Merck, Sharp & Dohme Corp.	Treatment of primary mediastinal B cell lymphoma	KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy	6/13/2018
n/a	Moxidectin	Medicines Development Limited	Treatment of onchocerciasis volvulus in children and adults	Moxidectin Tablets are indicated for the treatment of onchocerciasis due to Onchocerca volvulus in patients aged 12 years and older	6/13/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of primary peritoneal carcinoma	In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Venclexta	Venetoclax	AbbVie, Inc	Treatment of chronic lymphocytic leukemia	VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) without 17p deletion, who have received at least one prior therapy	06-08-2018
Rituxan(R); Mabthera (R)	Rituximab	Genentech, Inc	Treatment of pemphigus vulgaris	RITUXAN is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris	06-07-2018
Palynziq	Pegvaliase-pqpz	BioMarin Pharmaceutical Inc.	Treatment of hyper phenylalaninemia	Palynziq is indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management	05/24/2018
n/a	Tacrolimus granules for oral suspension	Astellas Pharma Global Development, Inc.	Prevention of rejection in kidney, liver or heart transplant in pediatric patients	PROGRAF Granules (tacrolimus for oral suspension) for the prevention of rejection in heart, kidney or liver transplant in pediatric patients	05/24/2018
Actemra	Tocilizumab	Genentech, Inc	Treatment of pediatric patients (age 16 years and	ACTEMRA® (tocilizumab) for subcutaneous injection is indicated for the treatment of	05-11-2018

			younger) with polyarticular-course juvenile idiopathic arthritis	active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older	
Darzalex	Daratumumab	Janssen Biotech, Inc	Treatment of multiple myeloma	In combination with bortezomib, melphalen, and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	05-07-2018
Tafinlar(R) Capsules And Mekinist(R) Tablets	Dabrafenib and trametinib	Novartis Pharmaceuticals Corporation	Treatment of patients with anaplastic thyroid cancer and locally advanced or metastatic papillary thyroid cancer whose tumors harbor a BRAF V600 mutation	TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options	05-04-2018
Tafinlar(R) Capsules And Mekinist(R) Tablets	Dabrafenib and trametinib	Novartis Pharmaceuticals Corporation	Treatment of patients with anaplastic thyroid cancer and locally advanced or metastatic papillary thyroid cancer whose tumors harbor a BRAF V600 mutation.	MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options	05-04-2018
Andexxa	Coagulation factor Xa (recombinant), inactivated-zhzo	Portola Pharmaceutical, Inc.	For reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent or emergent surgery	Coagulation factor Xa (recombinant), inactivated-zhzo is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding	05-03-2018
Kymriah	Tisagenlecleucel-T	Novartis Pharmaceuticals Corporation	Treatment of diffuse large B-cell lymphoma	KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients with diffuse large B-cell lymphoma, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma who received two or more lines of systemic therapy	05-01-2018
Mekinist And Tafinlar	Trametinib and dabrafenib	Novartis Pharmaceuticals Corporation	Treatment of Stage IIb through IV melanoma.	MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection	04/30/2018
Mekinist And Tafinlar	Trametinib and dabrafenib	Novartis Pharmaceuticals Corporation	Treatment of Stage IIb through IV melanoma.	TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection	04/30/2018
Jynarque	Tolvaptan	Otsuka Pharmaceuticals Co., Ltd.	Treatment of autosomal dominant polycystic kidney disease	JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)	04/23/2018
Tagrisso	Osimertinib	AstraZeneca Pharmaceuticals LP	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	TAGRISSO® is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test	04/18/2018
n/a	Fostamatinib disodium hexahydrate	Rigel Pharmaceutical, Inc.	Treatment of immune thrombocytopenic purpura	TAVALISSE is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to previous treatment.	04/17/2018
Crysvita	Burosumab-twza	Ultragenyx Pharmaceutical, Inc.	Treatment of X-linked hypophosphatemia (formerly known as vitamin D-resistant rickets)	CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older	04/17/2018
n/a	Recombinant von Willebrand factor (rhVWF)	Baxalta US, Inc.	Treatment of von Willebrand disease.	Indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for perioperative management of	04/13/2018

				bleeding	
Afinitor	Everolimus	Novartis Pharmaceuticals Corp.	Treatment of tuberous sclerosis complex including TSC-associated subependymal giant cell astrocytoma (SEGA), TSC-associated angiomyolipoma and TSC-associated lymphangioleiomyomatosis (LAM)	For the adjunctive treatment of adult and pediatric patients, age 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures	04-10-2018
Rubraca	Rucaparib	Clovis Oncology, Inc.	Treatment of ovarian cancer	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	04-06-2018
Leukine	Sargramostim	Partner Therapeutics, Inc.	Treatment of individuals acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)	LEUKINE® is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS])	03/29/2018
Blincyto	Blinatumomab	Amgen, Inc.	Treatment of acute lymphocytic leukemia	BLINCYTO® is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children	03/29/2018
Tasigna	Nilotinib	Novartis Pharmaceutical Corporation	Treatment of chronic myelogenous leukemia	TASIGNA® (nilotinib) is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase and pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy.	03/22/2018
Adcetris	Brentuximab vedotin	Seattle Genetics, Inc.	Treatment of Hodgkin's lymphoma	ADCETRIS® is indicated for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy.	03/20/2018
Hizentra	Immune Globulin Subcutaneous (Human), 20% Liquid	CSL Behring	Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP)	Indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIPD) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.	03/15/2018
Trogarzo	Ibalizumab	TaiMed Biologics, Inc.	Treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy	TROGARZO, in combination with another antiretroviral (s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen	03-06-2018
n/a	Tezacaftor and Ivacaftor combination therapy	Vertex Pharmaceuticals Inc.	Treatment of cystic fibrosis (CF)	SYMDEKO a combination of tezacaftor and ivacaftor, is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in-vitro* data and/or clinical evidence	02-12-2018
n/a	Tezacaftor and Ivacaftor combination therapy	Vertex Pharmaceuticals Inc.	Treatment of cystic fibrosis (CF)	YMDEKO a combination of tezacaftor and ivacaftor, is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane	02-12-2018

				conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in-vitro* data and/or clinical evidence	
n/a	lutetium Lu 177 dotatate	Advanced Accelerator Applications	Treatment of gastro-entero-pancreatic neuroendocrine tumors	Treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults	01/26/2018
Trisenox	Arsenic trioxide	Teva Branded Pharmaceutical Products R&D, Inc	Treatment of acute promyelocytic leukemia	In combination with tretinoin for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression	01/12/

2. Conclusion

The orphan drug programs relating to rare diseases have met success only in some countries. In a market where first-mover advantages are small, it is difficult to find the appropriate incentive system.

The system created by the ODA has led to an increase in the development, approval, and availability of orphan products. While the market exclusivity provision has expanded access to orphan drugs, it may be erroneously providing exclusive market protection for other products.

A country should try to produce important drugs for the benefit of the whole world, depending on the R and D investment, the return on such investment, the tax and patent incentives, and its regulatory policies. Agreement of these points might lead to beneficial changes in our national thinking and prevent "orphanisation of new drugs."[3]

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